

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074796

Trade Name : GUANFACINE HCL TABLETS

Generic Name: Guanfacine Hcl Tablets 1mg and 2mg USP

Sponsor : Mylan Pharmacueticals, Inc.

Approval Date: January 21, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074796

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074796

APPROVAL LETTER

9 n
ANDA 74-796

JAN 21

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road, P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated December 5, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Guanfacine Hydrochloride Tablets USP, 1 mg and 2 mg (base).

Reference is also made to your amendments dated June 11, June 27, July 29, and October 14, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Guanfacine Hydrochloride Tablets USP, 1 mg and 2 mg (base) to be bioequivalent and therefore, therapeutically equivalent to those of the listed drug (Tenex[®] Tablets, 1 mg and 2 mg (base) respectively, of A.H. Robins Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074796

FINAL PRINTED LABELING

MYLAN PHARMACEUTICALS INC.

GUANFACINE TABLETS, 1MG
ANDA 74-796

Each tablet contains guanfacine hydrochloride equivalent to 1 mg of guanfacine.

1 mg

N 0378-1160-01 8

MYLAN®

NDC 0378-1160-01

GUANFACINE TABLETS, USP

1 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: For dosage and other prescribing information, see accompanying product literature.

Mylan Pharmaceuticals Inc.
Bergantown, WV 26006

RN1160A

Each tablet contains guanfacine hydrochloride equivalent to 1 mg of guanfacine.

1 mg

N 0378-1160-01 8

MYLAN®

NDC 0378-1160-01

GUANFACINE TABLETS, USP

1 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: For dosage and other prescribing information, see accompanying product literature.

Mylan Pharmaceuticals Inc.
Bergantown, WV 26006

RN1160A

Each tablet contains guanfacine hydrochloride equivalent to 1 mg of guanfacine.

1 mg

N 0378-1160-01 8

MYLAN®

NDC 0378-1160-01

GUANFACINE TABLETS, USP

1 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Usual Dosage: For dosage and other prescribing information, see accompanying product literature.

Mylan Pharmaceuticals Inc.
Bergantown, WV 26006

RN1160A

Each tablet contains guanfacine hydrochloride equivalent to 1 mg of guanfacine.

1 mg

N 0378-1160-01 8

MYLAN®

NDC 0378-1160-01

GUANFACINE TABLETS, USP

1 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

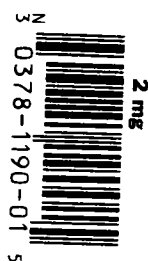
Usual Dosage: For dosage and other prescribing information, see accompanying product literature.

Mylan Pharmaceuticals Inc.
Bergantown, WV 26006

RN1160A

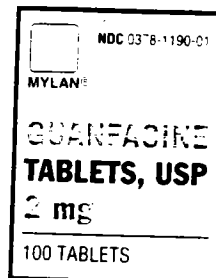
MYLAN PHARMACEUTICALS INC.

GUANFACINE TABLETS, 2MG
ANDA 74-796



Each tablet contains
guanfacine hydrochloride
equivalent to 2 mg of
guanfacine.

2 mg



CAUTION: Federal law
prohibits dispensing
without prescription.

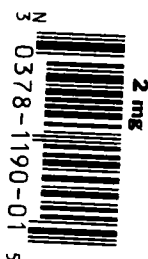
Dispense in a light
light-resistant container
as defined in the USP
using a child-resistant closure.

**STORE AT CONTROLLED
ROOM TEMPERATURE**
15°-30°C (59°-86°F).

Usual Dosage: For dosage and
other prescribing information,
see accompanying product
literature.

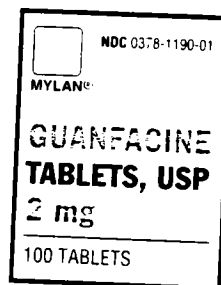
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1190A



Each tablet contains
guanfacine hydrochloride
equivalent to 2 mg of
guanfacine.

2 mg



CAUTION: Federal law
prohibits dispensing
without prescription.

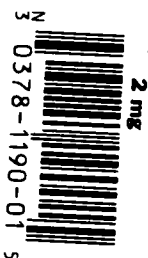
Dispense in a light
light-resistant container
as defined in the USP
using a child-resistant closure.

**STORE AT CONTROLLED
ROOM TEMPERATURE**
15°-30°C (59°-86°F).

Usual Dosage: For dosage and
other prescribing information,
see accompanying product
literature.

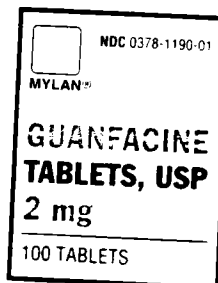
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1190A



Each tablet contains
guanfacine hydrochloride
equivalent to 2 mg of
guanfacine.

2 mg



CAUTION: Federal law
prohibits dispensing
without prescription.

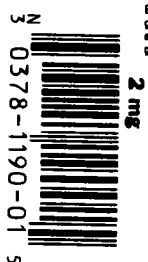
Dispense in a light
light-resistant container
as defined in the USP
using a child-resistant closure.

**STORE AT CONTROLLED
ROOM TEMPERATURE**
15°-30°C (59°-86°F).

Usual Dosage: For dosage and
other prescribing information,
see accompanying product
literature.

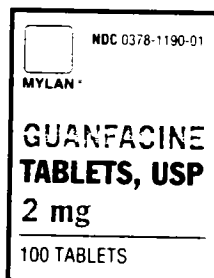
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1190A



Each tablet contains
guanfacine hydrochloride
equivalent to 2 mg of
guanfacine.

2 mg



CAUTION: Federal law
prohibits dispensing
without prescription.

Dispense in a light
light-resistant container
as defined in the USP
using a child-resistant closure.

**STORE AT CONTROLLED
ROOM TEMPERATURE**
15°-30°C (59°-86°F).

Usual Dosage: For dosage and
other prescribing information,
see accompanying product
literature.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM1190A

8

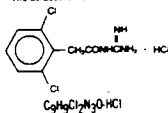


SPECIALTY

GUANFACINE TABLETS, USP 1 mg and 2 mg

DESCRIPTION: Guanfacine hydrochloride is a centrally acting antihypertensive with α_1 -adrenoreceptor antagonist properties in tablet form for oral administration.

The structural formula is:



The chemical name of guanfacine hydrochloride is N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride and its molecular weight is 282.56.

Guanfacine hydrochloride is a white to off-white powder, sparingly soluble in water and alcohol and slightly soluble in acetone.

Each tablet, for oral administration, contains guanfacine hydrochloride equivalent to 1 or 2 mg of guanfacine and the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. In addition, the 2 mg tablets contain the following ingredient: FD&C Blue #1 Aluminum Lake.

CLINICAL PHARMACOLOGY: Guanfacine hydrochloride is an orally active antihypertensive agent whose principal mechanism of action appears to be stimulation of central α_1 -adrenergic receptors. By stimulating these receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

The dose-response relationship for blood pressure and adverse effects of guanfacine given once a day as monotherapy has been evaluated in patients with mild to moderate hypertension. In this study patients were randomized to placebo or to 0.5 mg, 1 mg, 2 mg, 3 mg or 5 mg of guanfacine hydrochloride. Results are shown in the following table. A useful effect was not observed overall until doses of 2 mg were reached, although responses in white patients were seen at 1 mg. 24 hour effectiveness of 1 mg to 3 mg doses was documented using 24 hour ambulatory monitoring. While the 5 mg dose added an increment of effectiveness, it caused an unacceptable increase in adverse reactions.

Mean Changes (mm Hg) from Baseline in Seated Systolic and Diastolic Blood Pressure for Patients Completing 4 to 8 Weeks of Treatment with Guanfacine Monotherapy							
Mean Change	n	Placebo	0.5 mg	1 mg	2 mg	3 mg	5 mg
Systolic							
White Patients	11/30	-1/5	-6/8	-8/9	-12/11	-15/12	-18/16
Black Patients	8/28	-3/5	0/2	-3/5	-7/7	-9/9	-19/15

were seen at 1 mg. 24 hour effectiveness of 1 mg to 3 mg doses was documented using 24 hour ambulatory monitoring. While the 5 mg dose added an increment of effectiveness, it caused an unacceptable increase in adverse reactions.

Mean Changes (mm Hg) from Baseline in Seated Systolic and Diastolic Blood Pressure for Patients Receiving 1 to 3 mg of Treatment with Guanfacine Monotherapy*	
Mean Change	n
SD* Seated	63
Placebo	0.5 mg 1 mg 2 mg 3 mg
White Patients	11/5 -6/8 -8/9 -12/11 -15/12 -16/15
Black Patients	8/8 -3/5 -0/2 -3/5 -11/7 -8/9 -19/15

* SD = Systolic/diastolic blood pressure. Controlled clinical trials in patients with mild to moderate hypertension who were receiving a thiazide-type diuretic have defined the dose-response relationship for blood pressure response and adverse reactions of guanfacine given at bedtime and have shown that the blood pressure response to guanfacine can persist for 24 hours after a single dose. In the 12-week, placebo-controlled dose-response study, patients were randomized to placebo or to doses of 0.5, 1, 2, and 3 mg of guanfacine, in addition to 25 mg chlorthalidone, each given at bedtime. The observed mean changes from baseline, tabulated below, indicate the similarity of response for placebo and the 0.5 mg dose. Doses of 1, 2, and 3 mg resulted in decreased blood pressure in the sitting position with no real differences among the three doses. In the standing position there was some increase in response with dose.

Mean Decreases (mm Hg) in Seated and Standing Blood Pressure for Patients Treated with Guanfacine in Combination with Chlorthalidone	
Mean Change	n
SD* Seated	63
SD* Standing	63
Placebo	0.5 mg 1 mg 2 mg 3 mg
White Patients	-5/7 -5/6 -14/13 -12/13 -16/13
Black Patients	-3/5 -5/4 -11/9 -9/10 -15/12

* SD = Systolic/diastolic blood pressure. While most of the effectiveness of guanfacine in combination (and as monotherapy in white patients) was present at 1 mg, adverse reactions at this dose were not clearly distinguishable from those associated with placebo. Adverse reactions were clearly present at 2 and 3 mg (see Adverse Reactions).

In a second 12-week placebo-controlled study of 1, 2 or 3 mg of guanfacine hydrochloride administered with 25 mg of chlorthalidone once daily, a significant decrease in blood pressure was maintained for a full 24 hours after dosing. While there was no significant difference between the 12 and 24 hour blood pressure readings, the fall in blood pressure at 24 hours was numerically smaller, suggesting possible escape of blood pressure in some patients and the need for individualization of therapy.

In a double-blind, randomized trial, either guanfacine or clonidine was given at recommended doses with 25 mg chlorthalidone for 24 weeks and then abruptly discontinued. Results showed equal degrees of blood pressure reduction with the two drugs and there was no tendency for blood pressures to increase despite maintenance of the same daily dose of the two drugs. Signs and symptoms of rebound phenomena were infrequent upon discontinuation of either drug. Abrupt withdrawal of clonidine produced a rapid return of diastolic and especially, systolic blood pressure to approximately pre-treatment levels, with occasional values significantly greater than baseline, whereas guanfacine withdrawal produced a more gradual increase to pre-treatment levels, but also with occasional values significantly greater than baseline.

Pharmacodynamics: Hemodynamic studies in man showed that the decrease in blood pressure observed after single-dose or long-term oral treatment with guanfacine was accompanied by a significant decrease in peripheral resistance.

also with occasional values significantly greater than baseline.

Pharmacodynamics: Hemodynamic studies in man showed that the decrease in blood pressure observed after single-dose or long-term oral treatment with guanfacine was accompanied by a significant decrease in peripheral resistance and a slight reduction in heart rate (5 beats/min). Cardiac output under conditions of rest or exercise was not altered by guanfacine.

Guanfacine lowered elevated plasma renin activity and plasma catecholamine levels in hypertensive patients, but this does not correlate with individual blood-pressure responses.

Growth hormone secretion was stimulated with single oral doses of 2 and 4 mg of guanfacine. Long-term use of guanfacine had no effect on growth hormone levels.

Guanfacine had no effect on plasma aldosterone. A slight but insignificant decrease in plasma volume occurred after one month of guanfacine therapy. There were no changes in mean body weight or electrolytes.

Pharmacokinetics: Relative to an intravenous dose of 3 mg, the absolute oral bioavailability of guanfacine is about 80%. Peak plasma concentrations occur from 1 to 4 hours after with an average of 2.6 hours after single oral doses or at steady state.

The area under the concentration-time curve (AUC) increases linearly with the dose.

In individuals with normal renal function, the average elimination half-life is approximately 17 hr (range 10-30 hr). Younger patients tend to have shorter elimination half-lives (13-14 hr) while older patients tend to have half-lives at the upper end of the range. Steady state blood levels were attained within 4 days in most subjects.

In individuals with normal renal function, guanfacine and its metabolites are excreted primarily in the urine. Approximately 50% (40-75%) of the dose is eliminated in the urine as unchanged drug; the remainder is eliminated mostly as conjugates of metabolites produced by oxidative metabolism of the aromatic ring.

The guanfacine-to-creatinine clearance ratio is greater than 1, which would suggest that tubular secretion of drug occurs.

The drug is approximately 70% bound to plasma proteins, independent of drug concentration.

The whole body volume of distribution is high (a mean of 6.3 L/kg), which suggests a high distribution of drug to the tissues.

The clearance of guanfacine in patients with varying degrees of renal insufficiency is reduced, but plasma levels of drug are only slightly increased compared to patients with normal renal function. When prescribing for patients with renal impairment, the low end of the dosing range should be used. Patients on dialysis also can be given usual doses of guanfacine hydrochloride as the drug is poorly dialyzed.

INDICATIONS AND USAGE: Guanfacine tablets are indicated in the management of hypertension. Guanfacine may be given alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

CONTRAINDICATIONS: Guanfacine hydrochloride is contraindicated in patients with known hypersensitivity to guanfacine hydrochloride.

PRECAUTIONS: General: Like other antihypertensive agents, guanfacine should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal or hepatic failure.

Sedation: Guanfacine, like other orally active central α_2 -adrenergic agonists, causes sedation or drowsiness, especially when beginning therapy. These symptoms are dose-related (see Adverse Reactions). When guanfacine is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Rebound: Abrupt cessation of therapy with orally active central α_2 -adrenergic agonists may be associated with increases (from depressed on-therapy levels) in plasma and urinary catecholamines, symptoms of "nervousness and anxiety," and, less commonly, increases in blood pressure to levels significantly greater than those prior to therapy.

Information for Patients: Patients who receive guanfacine should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests: In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with guanfacine.

Drug Interactions: The following are

significantly greater than those prior to therapy.

Information for Patients: Patients who receive guanfacine should be advised to exercise caution when operating dangerous machinery or driving motor vehicles until it is determined that they do not become drowsy or dizzy from the medication. Patients should be warned that their tolerance for alcohol and other CNS depressants may be diminished. Patients should be advised not to discontinue therapy abruptly.

Laboratory Tests: In clinical trials, no clinically relevant laboratory test abnormalities were identified as causally related to drug during short-term treatment with guanfacine.

Drug Interactions: The potential for increased sedation when guanfacine is given with other CNS-depressant drugs should be appreciated.

The administration of guanfacine concomitantly with a known microsomal enzyme inducer (phenobarbital or phenytoin) to two patients with renal impairment reportedly resulted in significant reductions in elimination half-life and plasma concentration. In such cases, therefore, more frequent dosing may be required to achieve or maintain the desired hypotensive response. Further, if guanfacine is to be discontinued in such patients, careful tapering of the dosage may be necessary in order to avoid rebound phenomena (see Rebound above).

Anticoagulants: Ten patients who were stabilized on oral anticoagulants were given guanfacine, 1 to 2 mg/day, for 4 weeks. No changes were observed in the degree of anticoagulation.

In several well-controlled studies, guanfacine was administered together with diuretics with no drug interactions reported. In the long-term safety studies, guanfacine was given concomitantly with many drugs without evidence of any interactions. The principal drugs given (number of patients in parentheses) were: cardiac glycosides (115), sedatives and hypnotics (103), coronary vasodilators (52), oral hypoglycemics (45), cough and cold preparations (45), NSAIDs (38), antihyperlipidemics (29), antitumor drugs (24), oral contraceptives (18), bronchodilators (13), insulin (10), and beta blockers (10).

Drug/Laboratory Test Interactions: No laboratory test abnormalities related to the use of guanfacine have been identified.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenic effect was observed in studies of 78 weeks in mice at doses more than 150 times the maximum recommended human dose and 102 weeks in rats at doses more than 100 times the maximum recommended human dose. In a variety of test models, guanfacine was not mutagenic.

No adverse effects were observed in fertility studies in male and female rats.

Pregnancy Category B: Administration of guanfacine to rats at 70 times the maximum recommended human dose and to rabbits at 20 times the maximum recommended human dose resulted in no evidence of harm to the fetus. Higher doses (100 and 200 times the maximum recommended human dose in rabbits and rats respectively) were associated with reduced fetal survival and maternal toxicity. Rat experiments have shown that guanfacine crosses the placenta.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Guanfacine is not recommended in the treatment of acute hypertension associated with toxemia of pregnancy. There is no information available on the effects of guanfacine on the course of labor and delivery.

Nursing Mothers: It is not known whether guanfacine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when guanfacine hydrochloride is administered to a nursing woman. Experiments with rats have shown that guanfacine is excreted in the milk.

Pediatric Use: Safety and effectiveness in pediatric patients under 12 years of age have not been demonstrated. Therefore, the use of guanfacine in this age group is not recommended.

ADVERSE REACTIONS: Adverse reactions noted with guanfacine are similar to those of other drugs of the central α_2 -adrenoreceptor agonist class: dry mouth, sedation (somnolence), weakness (asthenia), dizziness, constipation, and impotence. While the reactions are common, most are mild and tend to disappear on continued dosing.

Skin rash with exfoliation has been reported in a few cases. Although clear cause and effect relationships to guanfacine could not be established, should a rash occur, guanfacine should be discontinued and the patient monitored appropriately.

In the dose-response monotherapy study described under Clinical Pharmacology, the frequency of the most commonly observed adverse reactions showed a dose relationship from 0.5 to 3 mg as follows:

Adverse Reaction	Placebo n=59	0.5 mg n=60	1 mg n=61	2 mg n=60	3 mg n=59
Dry Mouth	0%	10%	10%	42%	54%
Somnolence	0%	5%	10%	13%	39%
Asthenia	0%	2%	5%	7%	3%
Dizziness	0%	12%	7%	5%	13%
Headache	0%	12%	7%	5%	3%
Impotence	0%	0%	0%	7%	15%
Constipation	0%	2%	5%	5%	10%
Fatigue	2%	2%	5%	8%	10%

The percent of patients who dropped out because of adverse reactions are shown below for each dosage group.

Percent dropouts	Placebo	0.5 mg	1 mg	2 mg	3 mg
	0%	2.0%	5.0%	13%	32%

The most common reasons for dropouts among patients who received guanfacine were dry mouth, somnolence, dizziness, fatigue, weakness, and constipation.

In the 12-week, placebo-controlled, dose-response study of guanfacine administered with 25 mg chlorothalidone at bedtime, the frequency of the most commonly observed adverse reactions showed a clear dose relationship from 0.5 to 3 mg as follows:

Adverse Reaction	Placebo n=73	0.5 mg n=72	1 mg n=72	2 mg n=72	3 mg n=72
Dry Mouth	5 (7%)	4 (5%)	6 (8%)	8 (11%)	20 (28%)
Somnolence	1 (1%)	2 (3%)	0 (0%)	2 (3%)	10 (14%)
Asthenia	1 (1%)	2 (3%)	0 (0%)	2 (3%)	7 (10%)
Dizziness	2 (3%)	1 (1%)	3 (4%)	6 (8%)	3 (4%)
Headache	3 (4%)	4 (5%)	3 (4%)	1 (1%)	2 (3%)
Impotence	1 (1%)	1 (1%)	0 (0%)	1 (1%)	3 (4%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Fatigue	3 (4%)	2 (3%)	2 (3%)	5 (6%)	3 (4%)

There were 41 premature terminations because of adverse reactions in this study. The percent of patients who dropped out and the dose at which the dropout occurred were as follows:

Dose	Percent dropouts
Placebo	6.9%
0.5 mg	4.2%
1 mg	3.2%
2 mg	6.9%
3 mg	8.3%

Reasons for dropouts among patients who received guanfacine were:

1 mg 1 mg
3 mg 3 mg
3 mg 3 mg

Reasons for dropouts among patients who received guanfacine were somnolence, headache, weakness, dry mouth, dizziness, impotence, insomnia, constipation, syncope, urinary incontinence, conjunctivitis, paresthesia, and dermatitis.

In a second 12-week placebo-controlled combination therapy study in which the dose could be adjusted upward to 3 mg per day in 1-mg increments at 3-week intervals, i.e., a setting more similar to ordinary clinical use, the most commonly recorded reactions were dry mouth, 47%; constipation, 16%; fatigue, 12%; somnolence, 10%; asthenia, 6%; dizziness, 5%; headache, 4%; and insomnia, 4%.

Reasons for dropouts among patients who received guanfacine were somnolence, dry mouth, dizziness, impotence, constipation, confusion, depression, and palpitations.

In the clonidine/guanfacine comparison described in Clinical Pharmacology, the most common adverse reactions noted were as follows:

	Guanfacine (n=278)	Clonidine (n=278)
Adverse Reactions	30%	37%
Dry Mouth	21%	35%
Somnolence	11%	8%
Dizziness	11%	5%
Constipation	9%	8%
Fatigue	6%	4%
Headache	4%	3%
Insomnia	4%	3%

Adverse reactions occurring in 3% or less of patients in the three controlled trials of guanfacine with a diuretic were:

Cardiovascular: bradycardia, palpitations, substernal pain

Gastrointestinal: abdominal pain, diarrhea, dyspepsia, dysphagia, nausea

CNS: amnesia, confusion, depression, insomnia, libido decrease

ENT disorders: rhinitis, taste perversion, tinnitus

Eye disorders: conjunctivitis, iritis, vision disturbance

Musculoskeletal: leg cramps, hypokalemia

Respiratory: dyspnea

Dermatologic: dermatitis, pruritus, purpura, sweating

Urogenital: testicular disorder, urinary incontinence

Other: malaise, paresthesia, paresis

Adverse reaction reports tend to decrease over time. In an open-label trial of one year's duration, 560 hypertensive subjects were given guanfacine, titrated to achieve goal blood pressure, alone (51%), with diuretic (38%), with beta blocker (3%), with diuretic plus beta blocker (6%), or with diuretic plus vasodilator (2%). The mean daily dose of guanfacine reached was 4.7 mg.

	Incidence of adverse reactions at any time during the study n = 560	Incidence of adverse reactions at end of one year n = 368
Dry Mouth	62%	15%
Dizziness	31%	6%
Constipation	15%	1%
Fatigue	15%	1%
Headache	1%	0.2%
Insomnia	4%	0%

There were 52 (9%) dropouts due to adverse effects in this 1-year trial. The causes were: dry mouth (n = 20), weakness (n = 12), constipation (n = 7), somnolence (n = 3), nausea (n = 3), orthostatic hypotension (n = 2), insomnia (n = 1), rash (n = 1), nightmares (n = 1), headache (n = 1), and depression (n = 1).

Postmarketing Experience: An open-label postmarketing study involving 21,718 patients was conducted to assess the safety of guanfacine (as the hydrochloride) 1 mg/day given at bedtime for 28 days. Guanfacine was administered with or without other antihypertensive agents. Adverse events reported in the postmarketing study at an incidence greater than 1% included dry mouth, dizziness, somnolence, fatigue, headache and nausea. The most commonly reported adverse events in this study were the same as those observed in controlled clinical trials.

Less frequent, possibly guanfacine-related events observed in the postmarketing study and/or reported spontaneously include:

Body as a Whole: asthenia, chest pain, edema, malaise, tremor
Cardiovascular: heart rate > 100/min.

21,718 patients was conducted to assess the safety of guanfacine (as the hydrochloride) 1 mg/day given at bedtime for 28 days. Guanfacine was administered with or without other antihypertensive agents. Adverse events reported in the postmarketing study at an incidence greater than 1% included dry mouth, dizziness, somnolence, fatigue, headache and nausea. The most commonly reported adverse events in this study were the same as those observed in controlled clinical trials.

Less frequent, possibly guanfacine-related events observed in the postmarketing study and/or reported spontaneously include:

Body as a Whole: asthenia, chest pain, edema, malaise, tremor

Cardiovascular: bradycardia, palpitations, syncope, tachycardia

Central Nervous System: paresthesias, vertigo

Eye Disorders: blurred vision

Gastrointestinal System: abdominal pain, constipation, diarrhea, dyspepsia

Liver and Biliary System: abnormal liver function tests

Musculoskeletal System: arthralgia, leg cramps, leg pain, myalgia

Psychiatric: agitation, anxiety, confusion, depression, insomnia, nervousness

Reproductive System, Male: impotence

Respiratory System: dyspnea

Skin and Appendages: alopecia, dermatitis, exfoliative dermatitis, pruritus, rash

Special Senses: alterations in taste

Urinary System: nocturia, urinary frequency

Rare, serious disorders with no definitive cause and effect relationship to guanfacine have been reported spontaneously and/or in the postmarketing study. These events include acute renal failure, cardiac fibrillation, cerebrovascular accident, congestive heart failure, heart block, and myocardial infarction.

DRUG ABUSE AND DEPENDENCE: No reported abuse or dependence has been associated with the administration of guanfacine.

OVERDOSAGE: Signs and Symptoms: Drowsiness, lethargy, bradycardia and hypotension have been observed following overdose with guanfacine.

A 25-year-old female intentionally ingested 60 mg. She presented with severe drowsiness and bradycardia of 45 beats/minute. Gastric lavage was performed and an infusion of isoproterenol (0.8 mg in 12 hours) was administered. She recovered quickly and without sequelae.

A 28-year-old female who ingested 30 to 40 mg developed only lethargy, was treated with activated charcoal and a cathartic, was monitored for 24 hours, and was discharged in good health.

A 2-year-old male weighing 12 kg, who ingested up to 4 mg of guanfacine, developed lethargy. Gastric lavage (followed by activated charcoal and sorbitol slurry via NG tube) removed some tablet fragments within 2 hours after ingestion, and vital signs were normal. During 24-hour observation in ICU, systolic pressure was 58 and heart rate 70 at 16 hours post-ingestion. No intervention was required, and the child was discharged fully recovered the next day.

Treatment of Overdosage: Gastric lavage and supportive therapy as appropriate. Guanfacine is not dialyzable in clinically significant amounts (2.4%).

USAGE AND ADMINISTRATION: The recommended initial dose of guanfacine (as the hydrochloride) when given alone or in combination with another antihypertensive drug is 1 mg daily given at bedtime to minimize somnolence. If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, a dose of 2 mg may be given, although most of the effect of guanfacine is seen at 1 mg (see Clinical Pharmacology). Higher daily doses have been used, but adverse reactions increase significantly with doses above 3 mg/day.

The frequency of rebound hypertension is low, but it can occur. When rebound occurs, it does so after 2 to 4 days, which is delayed compared with clonidine hydrochloride. This is consistent with the longer half-life of guanfacine. In most cases, after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2 to 4 days) without ill effects.

HOW SUPPLIED: Guanfacine Tablets, USP equivalent to 1 or 2 mg of guanfacine are supplied as follows:

The 1 mg tablets are white, unscored, round tablets marked with M on one side and G4 on the other side. They are available as follows:

NDC 0378-1160-01
bottles of 100 tablets

The 2 mg tablets are blue, unscored, round tablets marked with M on one side and G5 on the other side. They are available as follows:

NDC 0378-1190-01
bottles of 100 tablets

STORE AT CONTROLLED ROOM TEMPERATURE 15° - 30°C (59° - 86°F).

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

9

Unlabeled After Approval: The recommended initial dose of guanfacine (as the hydrochloride) when given alone or in combination with another antihypertensive drug is 1 mg daily given at bedtime to minimize somnolence. If after 3 to 4 weeks of therapy, 1 mg does not give a satisfactory result, a dose of 2 mg may be given, although most of the effect of guanfacine is seen at 1 mg (see Clinical Pharmacology). Higher daily doses have been used, but adverse reactions increase significantly with doses above 3 mg/day.

The frequency of rebound hypertension is low, but it can occur. When rebound occurs, it does so after 2 to 4 days, which is delayed compared with clonidine hydrochloride. This is consistent with the longer half-life of guanfacine. In most cases, after abrupt withdrawal of guanfacine, blood pressure returns to pretreatment levels slowly (within 2 to 4 days) without ill effects.

HOW SUPPLIED: Guanfacine Tablets, USP equivalent to 1 or 2 mg of guanfacine are supplied as follows:

The 1 mg tablets are white, unscored, round tablets marked with M on one side and G4 on the other side. They are available as follows:

NDC 0378-1160-01
bottles of 100 tablets

The 2 mg tablets are blue, unscored, round tablets marked with M on one side and G5 on the other side. They are available as follows:

NDC 0378-1190-01
bottles of 100 tablets

STORE AT CONTROLLED ROOM TEMPERATURE 15° - 30°C (59° - 86°F).

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

CATION: Federal law prohibits dispensing without prescription.



MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED MAY 1996
GUAN.R1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074796

CHEMISTRY REVIEW(S)

Office of Generic Drugs
Chemistry, Manufacturing and Control Review

1. CHEMISTRY REVIEW NO: No. 2
2. ANDA: 74-796
3. NAME AND ADDRESS OF APPLICANT:
Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road, P.O. Box 4310
Morgantown, WV 26504-4310
4. LEGAL BASIS FOR SUBMISSION: See CR #1.
5. SUPPLEMENT(s): N/A
6. PROPRIETARY NAME: None
7. NONPROPRIETARY NAME: Guanfacine Tablets USP, 1 and 2 mg
8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A
9. AMENDMENTS AND OTHER DATES:
Mylan:
12/05/95 Submission of ANDA (received on 12/07/95)
12/13/95 Amendment (Labeling issue)
05/29/96* Telecon (Re: NA letter of 05/14/96)
06/27/96* Bio amendment (response to 04/23/96 bio letter)
06/11/96* Response to NA (MAJOR) letter of 05/14/96
07/29/96* Amendment to 06/11/96 submission
10/14/96* Minor amendment (bio issue).

FDA:
12/29/95 Acknowledgement letter
05/14/96 NA (MAJOR) letter (CR #1 by Steve Sherken)
10. PHARMACOLOGICAL CATEGORY: Antihypertensive
11. Rx or OTC: Rx
12. RELATED IND/NDA/DMF(s):
13. DOSAGE FORM:
1 mg strength: White, unscored, round tablets
marked with M on one side and G4 on the other.
2 mg strength: Blue, unscored, round tablets
marked with M on one side and G5 on the other.

14. **STRENGTH:** 1 mg and 2 mg
15. **CHEMICAL NAME AND STRUCTURE:** See CR #1
16. **RECORDS AND REPORTS:** N/A
17. **COMMENTS:** Confidential

TO FOIA PERSONNEL:

Do not release the comments below. The information provided below is for internal record use only.

On the first page of and again at the end of the cover letter of the 06/11/96 amendment, Mylan requested that the MAJOR AMENDMENT status be changed to MINOR AMENDMENT based on the reasons provided in the cover letter. There are no telephone records in the jacket or any handwritten comment (by OGD personnel) on the cover letter to show that the request was actually denied, or even considered. Obviously, the amendment was not reclassified to minor amendment which would have been reviewed on or around June 12, 1996 (the receiving date of the amendment). The request was denied under OGD Control 96-192.

It should be noted that this ANDA was first reviewed by Steve Sherken, was subsequently reclassified as a Random 2 during the week of 11/12/96 (re-assignment sheet is not found in the jacket), and was reassigned to this reviewer on 11/15/96. A copy has been placed in the jacket.

Mylan's response to the deficiencies cited in the last NA letter are all acceptable. They agreed to perform in-process test.

The USP has added new monographs in Supplement #4 to USP 23 for Guanfacine Hydrochloride and Guanfacine Tablets, pp. 3154-3156. When the CR #1 was reviewed, the review chemist of CR #1 was already aware of the USP status of Guanfacine Tablets and the NA letter contained appropriate comments.

Mylan's current methods and specifications that are used to analyze the drug substance are all now USP tests and specifications, except for test, which is an in-house test. Mylan's current tests and specifications for the drug product are all now USP tests and specifications, except the test for related substances, which is an in-house test and has been validated. In response to our comments in the last NA letter, Mylan has narrowed the specifications for related substances for product release and stability. Therefore, Mylan's specs conform to the first approved ANDA of Guanfacine Tablets, ANDA 74-145. Mylan's COAs for the

executed batches are based on the USP test methods. These methods have been validated by Mylan.

A bio deficiency letter has issued on 4/23/96. No further bio review document is found in the jacket. Labeling was found satisfactory in July 1996. EER is acceptable as of 06/12/96.

Since the drug product is a USP subject now, no method validation is needed.

18. CONCLUSIONS AND RECOMMENDATIONS:

Chemistry closed. If the final bio review is satisfactory, the ANDA will be approvable. Since this review is likely the last chemistry review before approval, composition table, specs for drug substance, drug product release and stability, container/closure summary, and manufacturing summary are included in the appropriate review sections for information purposes.

19. REVIEWER:

Shing H. Liu, Ph.D.

DATE COMPLETED:

11/20/1996

cc: ANDA 74-796
Division File
Field Copy

Endorsements:

HFD-625/SLiu/11/21/96
HFD-625/MSmela/11/25/96
X:\new\firmsam\mylan\ltrs&rev\74796CR2.MYL
F/t by: gp/11/27/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074796

BIOEQUIVALENCE REVIEW(S)

ANDA 74-796

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown WV 26504-4310
|||||


Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Guanfacine Tablets USP, 1 mg and 2 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23, supplement 4.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

 Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 17 1996

JIV

Guanfacine Hydrochloride

1 and 2 mg Tablets

ANDA #74-796

Reviewer: Kuldeep R. Dhariwal

Filename: 74796SDW.696

Mylan Pharmaceuticals Inc.

781 Chestnut Ridge Road

P.O. Box 4310

Morgantown

West Virginia 26504

Submission Date:

June 27, 1996

Oct 14, 1996

**Response to Review of Bioequivalence Study,
Dissolution Data and Waiver Request**

Mylan Pharmaceuticals, Inc. previously submitted a single-dose *in vivo* bioequivalence study under fasting conditions and dissolution data comparing its guanfacine hydrochloride, 2 mg tablets with reference listed drug Tenex® 2 mg tablets manufactured by A.H. Robins. The firm also requested waiver of *in vivo* bioequivalence study requirements for its 1 mg tablet. The bioequivalence study was found incomplete. The firm was asked to repeat dissolution testing, provide long-term stability of frozen samples and justify the choice of the Wagner equation as the regression equation. The comments were sent to the firm on April 23, 1996. The firm submitted the response as amendment on June 27, 1996 which was received by the Office of Generic Drugs on July 1, 1996. The amendment was assigned to this reviewer on September 12, 1996.

Response:

Comment 1. Data should be provided to support stability of the frozen samples at

Comment 2. Please justify the choice of the Wagner equation as the regression equation compared to other equation and weighting factors.

Comment 3. The comparative *in vitro* dissolution data comparing your test product to the reference listed drug have been reviewed and found acceptable. The dissolution studies were, however, conducted using 500 mL of dissolution medium (Water). You are advised that the office currently requires that the dissolution be conducted using 900 mL. We recognize that use of a volume of 500 mL should provide more discriminating evidence of quality, and is thus acceptable for use as an internal quality control. However, the use of 900 mL will need to be incorporated into your stability and quality control programs as a condition of approval.

Response: The dissolution studies conducted by Mylan using 500 mL of water were performed in accordance with the dissolution procedure listed in the official USP monograph for guanfacine tablets. This dissolution procedure was listed in the proposed monograph for guanfacine tablets which was contained in Sept.-Oct. 1992 Pharmacopeial Forum (p. 3853) and the May-June 1995 Pharmacopeial Forum (p. 686). The final monograph appeared in the Fourth Supplement to USP 23 (p. 3155), which became official on May 15, 1996. As the dissolution procedure in the official USP monograph for guanfacine tablets calls for the use of 500 mL of water and Mylan labels its product as USP we propose to continue using this procedure in our quality control and stability programs unless otherwise notified by the Agency.

Comments:

1. The samples in the bio-study were stored for The firm is documenting the stability of guanfacine in plasma for The stability data submitted by the firm are acceptable.
2. The use of Wagner equation as the regression equation is acceptable.
3. The fourth supplement dated May 15, 1996 to USP 23 gives following dissolution specifications for guanfacine tablets:

Medium: Water, 500 mL

Apparatus 2, 50 rpm

Tolerances: Not less than (Q) of the labeled amount of guanfacine is dissolved in 45 minutes.

The firm has followed these specifications. Since the fourth supplement to USP 23 recommends use of 500 mL instead of 900 mL water, the firm's use of 500 mL water is acceptable.

4. An inspection request for routine audit of the biostudy was issued to the FDA Division of Scientific Investigations. The final determination as to the acceptability of the study will depend in part upon the outcome of this data audit.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Mylan Pharmaceuticals Inc. on its 2 mg guanfacine tablet, lot #2B006A, comparing it to the reference listed drug, Tenex[®] tablet 2 mg, lot #0940605 manufactured by A.H. Robins has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Mylan's guanfacine 2 mg tablet is bioequivalent to the reference product Tenex[®] 2 mg tablet manufactured by A.H. Robins.
2. The dissolution testing conducted on guanfacine 1 mg and 2 mg tablets is acceptable. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 500 mL of water at 37° C using apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

APR 4 1996

DW

Guanfacine Hydrochloride

1 and 2 mg Tablets

ANDA #74-796

Reviewer: Kuldeep R. Dhariwal

Filename: 74796SDW.D95

Mylan Pharmaceuticals Inc.

781 Chestnut Ridge Road

P.O.Box 4310

Morgantown

West Virginia 26504

Submission Date:

December 5, 1995

Review of Bioequivalence Study, Dissolution Data and Waiver Request

The firm has submitted a single-dose *in vivo* bioequivalence study under fasting conditions and dissolution data comparing its guanfacine hydrochloride, 2 mg tablets with reference listed drug Tenex[®] 2 mg tablets manufactured by A.H.Robins. The firm has also requested waiver of *in vivo* bioequivalence study requirements for its 1 mg tablet. To support the request, the firm has submitted comparative dissolution profiles on 1 mg of its product and reference listed drug Tenex[®].

Introduction:

Guanfacine Hydrochloride is a centrally acting antihypertensive with α_2 -adrenoceptor agonist properties. Its principal mechanism of action appears to be stimulation of central α_2 -adrenergic receptors. By stimulating these receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

It is indicated in the management of hypertension and may be given alone or in combination with other antihypertensive agents. Relative to an intravenous dose of 3 mg, the absolute oral bioavailability of guanfacine is about 80%. Peak plasma concentrations occur from 1 to 4 hours with an average of 2.6 hours after single oral doses or at steady state. The area under the concentration-time curve increases linearly with dose. In individuals with normal renal function, the average elimination half-life is approx. 17 hr; the drug and its metabolites are excreted primarily in urine. The drug is about 70% bound to plasma proteins.

The recommended initial dose is 1 mg daily at bedtime to minimize somnolence. The reference listed drug is Tenex[®] manufactured by A.H.Robins and is available as 1 mg and 2 mg tablets.

Bioavailability of Guanfacine Hydrochloride 2 mg Tablet Under Fasting Conditions:

A. Objective:

The objective of this study is to compare the single dose bioavailability of Mylan and A.H.Robins (Tenex[®]) 2 mg guanfacine hydrochloride tablets.

B. Study Sites and Investigators:

Clinical Site:

Analytical Site:

Principal Investigator

Study Physician

Protocol #950112 "Comparative, randomized, single-dose, 2-way crossover bioavailability study of Mylan and A.H.Robins (Tenex[®]) 2 mg guanfacine hydrochloride tablets in healthy adult males under fasted conditions" was approved by the

Consent Form: A copy of the volunteer informed consent form used in the study is given on page 267, vol. 1.1.

Study Dates: Phase I June 10-14, 1995

Phase II June 24-28, 1995

Analysis Dates: October 12, 1995 to October 25, 1995

C. Study Design:

The study was designed as a randomized, two-treatment, crossover bioavailability study. The study was executed in two periods with a two week washout period between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at least 36 hours postdose each period. The subjects were assigned to two sequences at random as follows:

Sequence	Subject number	Phase I	Phase II
1	2, 4, 5, 6, 8, 11, 12, 15, 16, 17, 21, 22, 25	A	B
2	1, 3, 7, 9, 10, 13, 14, 18, 19, 20, 23, 24, 26	B	A

A: Guanfacine hydrochloride tablets, 1x2 mg; Mylan Pharmaceuticals Inc.; Lot #2B006A; Lot size: tablets; Manufacture Date: 02/95; Assay: 100.9%; Uniformity of Dosage Units: 100.9%.

B: Tenex⁹ tablets, 1x2 mg; A.H.Robins; Lot #0940605; Expiry Date: 03/96; Assay: 96.2%; Uniformity of Dosage Units: 95.8%.

The subjects fasted for 10 hours prior to dosing and until 5 hours postdose. Liquids were not allowed for two hours before and four hours after dosing. The drug products were administered with 240 mL of water. Subjects were dosed while seated in bed and remained seated in bed for the first 4 hours after drug administration. Sitting blood pressure and heart rate were measured predose and approximately 1,2,3,4,5,6,7,8,12,16,24,36, 48,72, and 96 hours after drug administration.

D. Subject selection:

Twenty-six healthy, non-smoking, male volunteers were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- 18-45 years of age, weighing at least 60 Kg, who are within 10% of their ideal weights (Table of "Desirable weights of adults", Metropolitan Life Insurance Company, 1983).
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits

Subjects were excluded from this study based on the following criteria:

- history or presence of significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease
- history or presence of significant alcoholism or drug abuse within the last year
- history or presence of significant hypersensitivity or idiosyncratic reaction to guanfacine hydrochloride or to other phenylacetyl-guanidine derivatives; hepatitis
- history or presence of significant tobacco or illegal drug use in any form during the previous 6 months
- blood pressure lower than 110/70 mm Hg at screening or 100/60 mm Hg at the time of the predose vital signs determination
- pulse of 50 b.p.m. or lower at screening or prior to dosing
- subjects on an abnormal diet during the four weeks preceding the study
- participation in another clinical trial within 28 days of study start
- subjects who, through completion of this study, would have donated more than 500 mL of blood in 14 days, 750 mL in 3 months, 1000 mL in 6 months, 1500 mL in 9 months or 2000 mL in a year

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days preceding the study or OTC medications for 7 days preceding the study
- no vitamin supplements for 48 hours preceding the study
- no alcohol or xanthine-containing beverages and food for 48 hours before dosing and throughout the period of sample collection

E. Sample Collection:

Blood samples were collected in Vacutainers containing EDTA before dosing (2x7 mL) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours after dosing (1x7 mL each). Samples were cooled in an ice bath and centrifuged under refrigeration as soon as possible.

F. Analytical Methods:

G. Pharmacokinetics/Statistical Analysis:

AUC_{0-t} , AUC_{0-inf} , C_{max} , T_{max} , kel , $t_{1/2}$ were calculated. Statistical analysis was performed using SAS. Analysis of variance was performed using the GLM procedure on the untransformed pharmacokinetic parameters. Additionally, log-transformed data were used for analysis of AUC_{0-t} , AUC_{0-inf} , and C_{max} . The analysis of variance model include sequence, subjects nested within sequence, period and drug formulation as factors. The significance of the sequence effect was tested using the subjects nested within sequence as the error term. A 5% level of significance was used for within-subject comparisons (period, formulation) and a 10% level of significance for between-subject comparisons (sequence). Each analysis of variance included calculation of geometric means, adjusted differences between formulation means and the

standard error associated with these differences. The two one-sided tests were used to estimate the 90% confidence intervals for AUC_{0-t} , AUC_{0-inf} and C_{max} , using both untransformed and transformed data.

H. Results:

1. Clinical:

Twenty-six subjects entered the study. Two subjects did not report for phase II dosing due to personal reasons and one subject withdrew from period I due to death in the family. Clinical vital signs were measured predose and approximately 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 24, 36, 48, 72 and 96 hours after drug administration. There were no clinically significant differences in these parameters between the test and reference formulations (Figures 1, 2).

Adverse events:

Following subjects experienced adverse events during the study for which no medication was required:

Subject #	Phase	Product	Sign/Symptom
3	I	reference	Nausea
7	I	reference	Nauseated from blood draws Hands feel tingly
8	II	reference	Headache
9	I	reference	Dizzy, lightheaded, faint
10	I	reference	Groggy
12	II	reference	Headache
17	II	reference	Fainted
18	I	reference	Headache Bruised right arm
23	I	reference	Headache Dull pain in left forearm
26	I	reference	Itching all over from stomach on up, Head hurts

Deviations in the study:

1. Food Intake: Subject #23 consumed 0.5 ounces of tea approximately one day prior to period 2 dosing. Subject #23 also consumed 2 beers and 1 can of coke between 2 and 3 days and between 3 and 4 days, respectively, after period 1 dosing. Subject #24 consumed 1 Twix candy bar 2.4 days after period 1 dosing. Subject #25 consumed 1/4 cup of tea 1.3 days prior to period 1 dosing. Subject #25 also consumed chocolate yogurt ice cream between 2 and 3 days after period 1 dosing.

2. Deviations from the blood sampling schedule: There were 86 deviations in blood sampling schedule involving all study subjects. Seventy-seven deviations were at the last three sampling times (48, 72, and 96 hours).

3. One sample (subject #19, period 2, 96 hour) was left in the centrifuge at room temperature for 2.9 days after the blood draw. As per the protocol, the blood sample should have been centrifuged immediately under refrigeration and plasma stored at -12°C or lower.

4. The protocol specified that subjects were to be housed from 12 hours before until 36 hours after drug administration. However, subject #15 and 24 were housed for 10.7 and 10.6 hours respectively, prior to period 2 dosing.

5. Deviations in sample processing: The sample analysis was repeated for all samples due to a processing error in the initial analysis. Samples proved to be unstable when reconstituted and left at room temperature for a period greater than 4.5 hours. Since some samples had been stored upto 11.5 hours after reconstitution and prior to all samples were reanalyzed under conditions (refrigeration) where reconstituted extract were proven stable. Subject #4 was reassayed and the run did not meet the acceptance criteria. The subject was not repeated due to insufficient volume of plasma. Due to the reassay, several samples were not reportable or had insufficient plasma volume for analysis:

53 samples were lost in processing

44 samples were not reportable

45 samples had insufficient plasma (no sample remaining)

03 no sample

01 poor chromatography

01 above upper limit of standard curve

Reassays: During the repeat analysis (above) 4 samples had anomalous values and so were reassayed. Three samples became not reportable and 1 sample was below limit of quantitation.

2. Analytical:

3. Pharmacokinetics/Statistics :

The mean plasma concentrations of guanfacine at each time point after test and reference products are shown in Table 1. Significant differences ($\alpha = 0.05$) in mean concentrations were observed at 2.5, 3, 3.5 and 96 hours. The time courses of guanfacine concentrations after the two products are plotted in Figures 3 and 4. The pharmacokinetic parameters are summarized in Table 2. There is no statistically significant difference between the two formulations for AUC_{0-t} and AUC_{0-inf} . However, significant difference (p value=0.046) was observed for C_{max} between the two formulations. AUC_{0-t} and AUC_{0-inf} of the test product were 2% and 1% higher than the respective parameters of the reference product. The C_{max} of the test product was 5% higher and occurred 12 minutes earlier.

The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Guanfacine Hydrochloride (Test)

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
5	97.847	101.667	97.848	101.666
8	106.632	113.210	106.633	113.209
17	105.00	109.026	105.003	109.031

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The individual mean ratios for AUC_{0-t} , AUC_{0-inf} , and C_{max} are summarized in Table 3. The test/reference ratios for AUC_{0-t} ranged from 0.73-1.97, AUC_{0-inf} ranged from 0.66-1.37, and C_{max} ranged from 0.84-1.29. Table 4 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from 0.72 to 0.96 (20 out of 22 values between 0.89 to 0.96) for test and 0.49-0.97 (20 out of 22 values between 0.85-0.97) for reference product.

The following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
LNAUC _{0-t}	95-110	95.41-110.13
LNAUC _{0-inf}	95-106	94.99-105.85
LNC _{max}	101-109	101.81-110.67

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125. Statistical analysis of data did not show any significant treatment, sequence or period effect for AUC_{0-t} and AUC_{0-inf}. However, there was statistically significant period (p=0.0035) and treatment effect (p=0.0228) for C_{max}.

***In Vitro* Dissolution Testing:**

The firm has submitted comparative dissolution data for test and reference products. The drug products used in the dissolution tests were from the same lots used in the *in vivo* bioequivalence studies. No USP dissolution method is available at this time. The method used by the firm is the same as described in the last FDA dissolution handbook except that the firm used 500 mL instead of 900 mL of water for dissolution testing.

Waiver Request:

The firm is requesting for a waiver of *in vivo* bioequivalence study for its 1 mg guanfacine tablets, under 21 CFR 320.22(d)(2). The comparative quantitative composition of 1 mg and 2 mg tablets is shown in Table 5. The 1 mg tablets are proportionally similar in their active and inactive ingredients to the 2 mg tablets. The dissolution profile of 1 mg test product is similar to 1 mg tablet of reference product. However, the firm would be asked to repeat dissolution tests using 900 mL water as recommended in last FDA dissolution hand book.

Comments:

1. Twenty-six subjects entered the study. Two subjects (#3 and 26) did not return for phase II due to personal reasons and one subject (#20) withdrew during period I due to death in family.

The analytical assay results from subject #4 did not meet the acceptance criteria; samples could not be reassayed due to insufficient volume of plasma. Therefore, results from subject #4 are not included. Results from twenty-two subjects are presented. Ten subjects experienced adverse effects (all while taking reference product). None of them required any medication. There were no clinically significant differences between the test and reference formulations in vital signs measured at predose and during the study.

2. There were 86 deviations in blood sampling schedule involving all study subjects. Subject #4 (3 deviations) was not included in data analysis because his assay results did not meet the acceptance criteria. Subject #26 (1 deviation) did not return for phase II. Seventy three deviations out of remaining 82 were at the last three sampling times (48, 72 and 96 hours). The remaining nine deviations were as follows:

Subject #	Treatment	Sampling time (h)	Deviation
16	Test	2.5	3 min. late
17	Test	2.5	4 min. late
24	Test	3.0	3 min. late
19	Test	12.0	sample time not recorded
1	Ref	3.5	3 min. late
2	Ref	6.0	21 min. late
22	Ref	4.0	8 min. late
23	Ref	2.0	4 min. late
23	Ref	2.5	3 min. late

This reviewer calculated $AUC_{0-\infty}$ for 4 subjects who had significant deviations in their blood sampling times. Following table shows that there is almost no difference in $AUC_{0-\infty}$ calculated using scheduled time vs. actual time:

Subject #	Treatment	Period	Scheduled time	$AUC_{0-\infty}$	Actual time
1	Test	2	80.324		80.255
5	Reference	2	88.990		88.911
15	Reference	2	79.368		79.300
22	Reference	2	81.622		81.460

3. The sample analysis was repeated for all samples due to a processing error in the initial analysis. Samples proved to be unstable when reconstituted and left at room temperature for a period greater than 4.5 hours. Since some samples had been stored upto 11.5 hours after reconstitution and prior to all samples were reanalyzed under conditions

(refrigeration) where reconstituted extracts were proven stable. The firm states that since none of the samples had undergone the freeze-thaw process more than the proven 3 freeze-thaw cycle stability, the results obtained should be reliable.

However, due to the reassay, 92 sample values (44 not reportable, 45 no sample remaining, and 3 no sample) are missing:

Following subjects have missing values near C_{max} :

Treatment A: Subject # 10, 12, 14 and 25

Treatment B: Subject # 2, 7, 8, 10, 14 and 25

In addition, following subjects do not have plasma values up to three half-lives of the drug (half-life is about 15 hours):

Treatment A

#2: no values after 16 h

#12: no values after 24 h

#25: only 7 values out of 19

Treatment B

#2: no values after 24 h

#25: no values after 16 h

The reviewer repeated statistical analysis after omitting all of the above subjects (#2,12,25,10,7,8,14). The 90% confidence intervals obtained were all within 80-125% limit:

LNAUC _{0-t}	98.0-108.2
LNAUC _{0-inf}	98.5-109.6
LNC _{max}	101.7-113.2

4. It is noted that curve DYK24 (subject 12) was accepted by extraordinary case according to SOP. The high QC samples did not meet the acceptance criteria (both values were outside $\pm 10\%$ of nominal concentration).

5. There is no statistically significant difference between the two formulations for AUC_{0-t} and AUC_{0-inf}. However, significant difference (p value=0.046) was observed for C_{max} between the two formulations. AUC_{0-t} and AUC_{0-inf} of the test product were 2% and 1% higher than the respective parameters of the reference product. The C_{max} of the test product was 5% higher and occurred 12 minutes earlier. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. Statistical analysis of data did not show any significant treatment, sequence or period effect for AUC_{0-t} and AUC_{0-inf}. However, there was statistically significant period (p=0.0035) and treatment effect (p=0.0228) for C_{max} .

6. The dissolution method used by the firm is the same as described in the last FDA dissolution handbook except that the firm used 500 mL instead of 900 mL of water for dissolution testing. The firm would be asked to repeat dissolution testing of test and reference products using 900 mL water.

7. Firm's 1 mg tablets are proportionally similar in their active and inactive ingredients to the 2 mg tablets except the colorant and a minor difference in the amount of lactose. However, the firm would be asked to submit dissolution data using 900 mL water as recommended in last FDA dissolution hand book.

8. An inspection request for routine audit of the biostudy is being issued to the FDA Division of Scientific Investigations from the Division of Bioequivalence. The final determination as to the acceptability of the study will depend in part upon the outcome of this data audit.

Deficiencies:

1. The dissolution testing of test and reference tablets (both strengths) should be repeated using 900 mL water and all other conditions the same.
2. The firm should provide data to support stability of frozen samples at -22°C for 137 days.
3. The firm should justify the choice of the Wagner equation as the regression equation compared to other equation and weighting factors.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Mylan Pharmaceuticals Inc. on its 2 mg guanfacine tablet, lot #2B006A, comparing it to the reference listed drug, Tenex[®] tablet 2 mg, lot #0940605 manufactured by A.H Robins has been found incomplete by the Division of Bioequivalence for the reasons given in the deficiencies.
2. The dissolution testing data are not acceptable for the reasons given in deficiency # 1.
3. The waiver of the *in vivo* bioequivalence study requirements for the firm's 1 mg tablet is denied pending approval of the 2 mg strength of the test product.

The firm should be informed of the deficiencies #1-3.

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED R.PATNAIK
FT INITIALED R.PATNAIK

Date 4/3/96

Concur:

Date 4/7/96

Keith Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74796 (original, duplicate), HFD-600 (Hare), HFD-630,
HFD-344 (CViswanathan), HFD-655 (Patnaik, Dhariwal), Drug File,
Division File

KRD/Draft: 032696; Final: 040296

Table 1

Mean Guanfacine Hydrochloride Plasma Concentrations (ng/mL)

Time (h)	Test			Reference			Test/Ref	Signifi.
	Mean	SE	N	Mean	SE	N		
0	0.0		21	0.0		22		
0.5	1.54	0.28	16	0.99	0.14	21	1.55	N.S.
1	2.94	0.21	22	2.71	0.21	21	1.08	N.S.
1.5	3.87	0.17	20	3.52	0.20	22	1.10	N.S.
2	3.96	0.18	19	3.81	0.21	20	1.04	N.S.
2.5	4.15	0.15	21	3.80	0.21	19	1.09	0.0249
3	4.04	0.13	18	3.70	0.14	15	1.09	0.0214
3.5	4.02	0.16	20	3.69	0.16	19	1.09	0.0011
4	3.95	0.14	19	3.76	0.17	22	1.05	N.S.
5	3.99	0.11	20	3.77	0.15	22	1.06	N.S.
6	3.56	0.11	22	3.37	0.10	22	1.06	N.S.
8	3.05	0.11	21	2.95	0.10	21	1.03	N.S.
12	2.49	0.10	21	2.43	0.11	22	1.02	N.S.
16	1.87	0.09	22	1.90	0.06	22	0.98	N.S.
24	1.29	0.06	20	1.28	0.06	20	1.00	N.S.
36	0.78	0.06	19	0.74	0.05	20	1.05	N.S.
48	0.41	0.03	20	0.42	0.04	17	0.98	N.S.
72	0.12	0.03	16	0.15	0.02	14	0.80	N.S.
96	0.01	0.01	13	0.02	0.02	13	0.50	0.0001

SE = Standard Error

Table 2

**Guanfacine Hydrochloride Plasma Concentrations: Pharmacokinetic
Parameters (N=22)**

Parameter	Test	Reference	Test/Ref	Confidence Interval
AUC_{0-t} (ng/mLxh)	81.09±20.27	79.43±21.40	1.02	97-107
AUC_{0-inf} (ng/mLxh)	87.40±18.84	86.87±18.02	1.01	96-105
C_{max} (ng/mL)	4.50±00.61	4.28±00.76	1.05	101-108
T_{max} (h)	2.89±01.14	3.09±01.34	0.94	
Half-life (h)	14.65±02.84	15.18±03.38	0.97	
KEL (h ⁻¹)	0.0494±0.012	0.0479±0.011	1.03	
$LNAUC_{0-t}$	4.36±0.26	4.34±0.30	1.00	95-110
$LNAUC_{0-inf}$	4.45±0.21	4.45±0.20	1.00	95-106
LNC_{max}	1.49±0.14	1.44±0.17	1.03	101-109

KEL = Elimination rate constant

Table 3

Test/Reference Ratios for Pharmacokinetic Parameters for Individual Subjects

Subject	Ratio		
	AUC _{0-t}	AUC _{0-inf}	C _{max}
1			
2			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
21			
22			
23			
24			
25			

Table 4

AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects

Subject	AUC _{0-t} /AUC _{0-inf} Ratio	
	Test	Reference
1		
2		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
21		
22		
23		
24		
25		

Table 5

Comparative Quantitative Composition of Guanfacine
1 mg and 2 mg Tablets

Ingredient	1 mg tablet		2 mg tablet	
	mg	%	mg	%
Guanfacine HCl	1.15	0.9	2.30	1.8
equiv. to guanfacine				
Lactose, anhy., NF				
Microcrystalline				
cellulose, NF				
FD&C Blue #1 Lake				
Magnesium Stearate/ Sodium lauryl sulfate				
Colloidal Silicon				
Dioxide, NF				
Total Tablet Weight	130.0	100.0	130.0	100.0
(Theoretical)				

Table 6. In Vitro Dissolution Testing

Drug (Generic Name): Guanfacine Tablets
Dose Strength: 1 and 2 mg
ANDA No.: 74796
Firm: Mylan Pharmaceuticals Inc.
Submission Date: December 5, 1995
File Name: 74796SDW.D95

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Water Volume: 500 mL
Specifications: NLT in 45 minutes
Reference Drug: Tenex[®] (AH Robins)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Min)	Test Product Lot # 2B006A Strength(mg) 2			Reference Product Lot # 0940605 Strength(mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
15	91		5.2	78		15.1
30	96		2.2	91		6.3
45	97		2.2	94		3.6

Sampling Times (Min)	Test Product Lot # 2B005A Strength(mg) 1			Reference Product Lot # 0941312 Strength(mg) 1		
	Mean %	Range	%CV	Mean %	Range	%CV
15	86		8.3	78		8.4
30	92		5.8	89		2.8
45	96		4.0	93		2.0

GUANFACINE HCL (GUAN-9510)

Mean Vital Signs Data
Blood Pressure

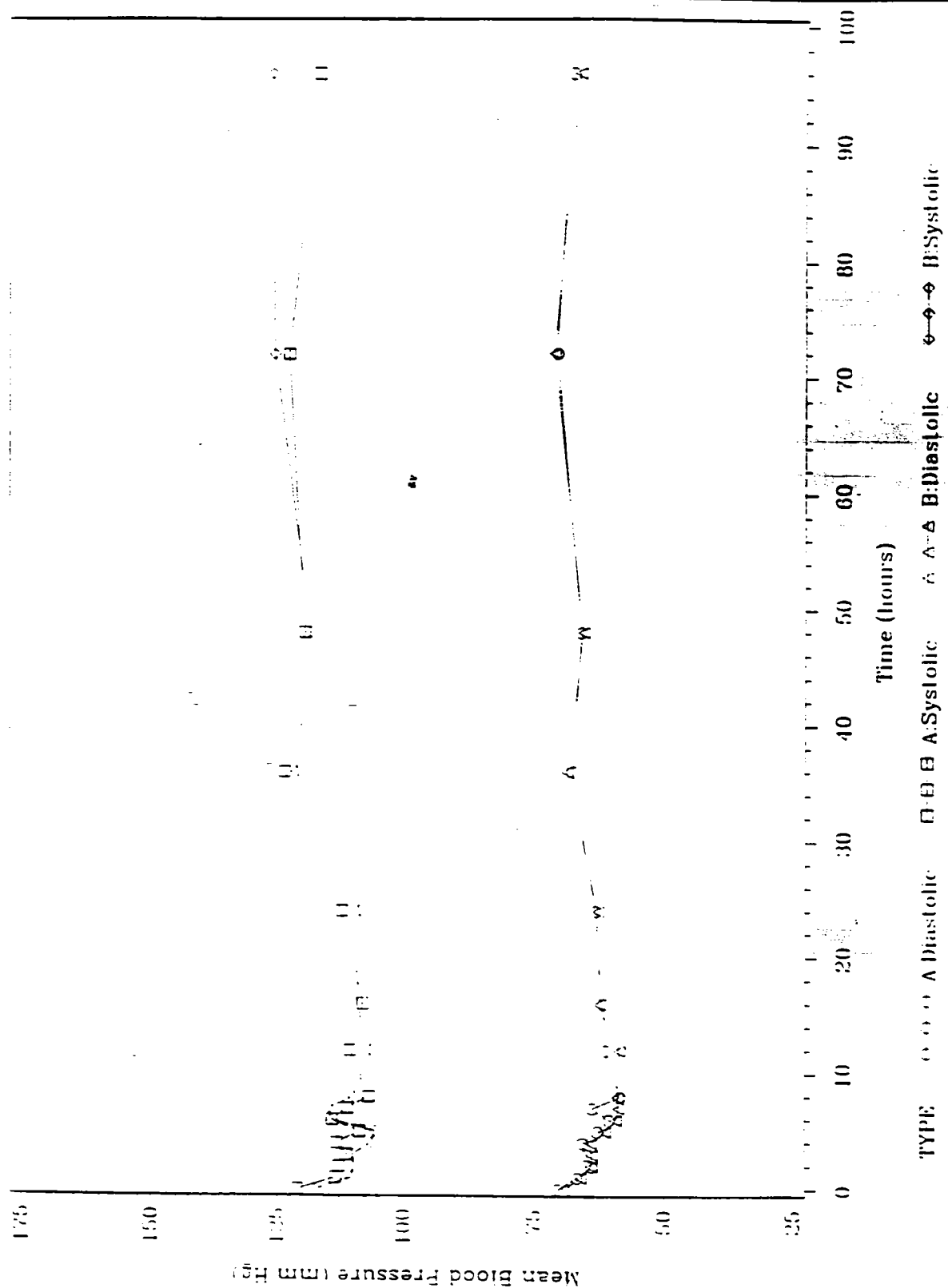


Fig. 1

GUANFACINE HCL (GUAN-9510)

Mean Vital Signs Data
Heart Rate

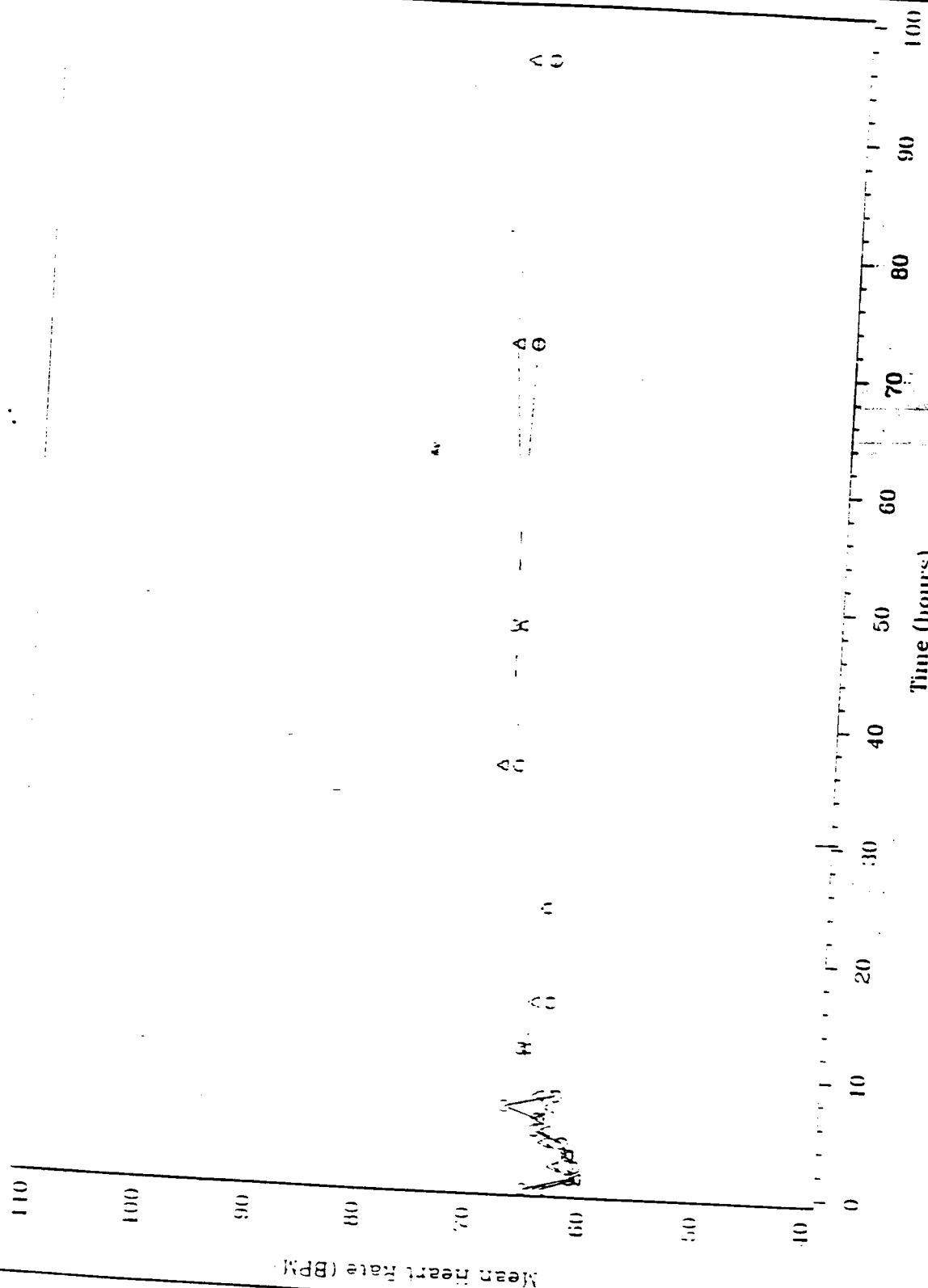


Fig. 2

2216

GUANFACINE HCl. (GUAN-9510) Mean Guanfacine Plasma Concentrations

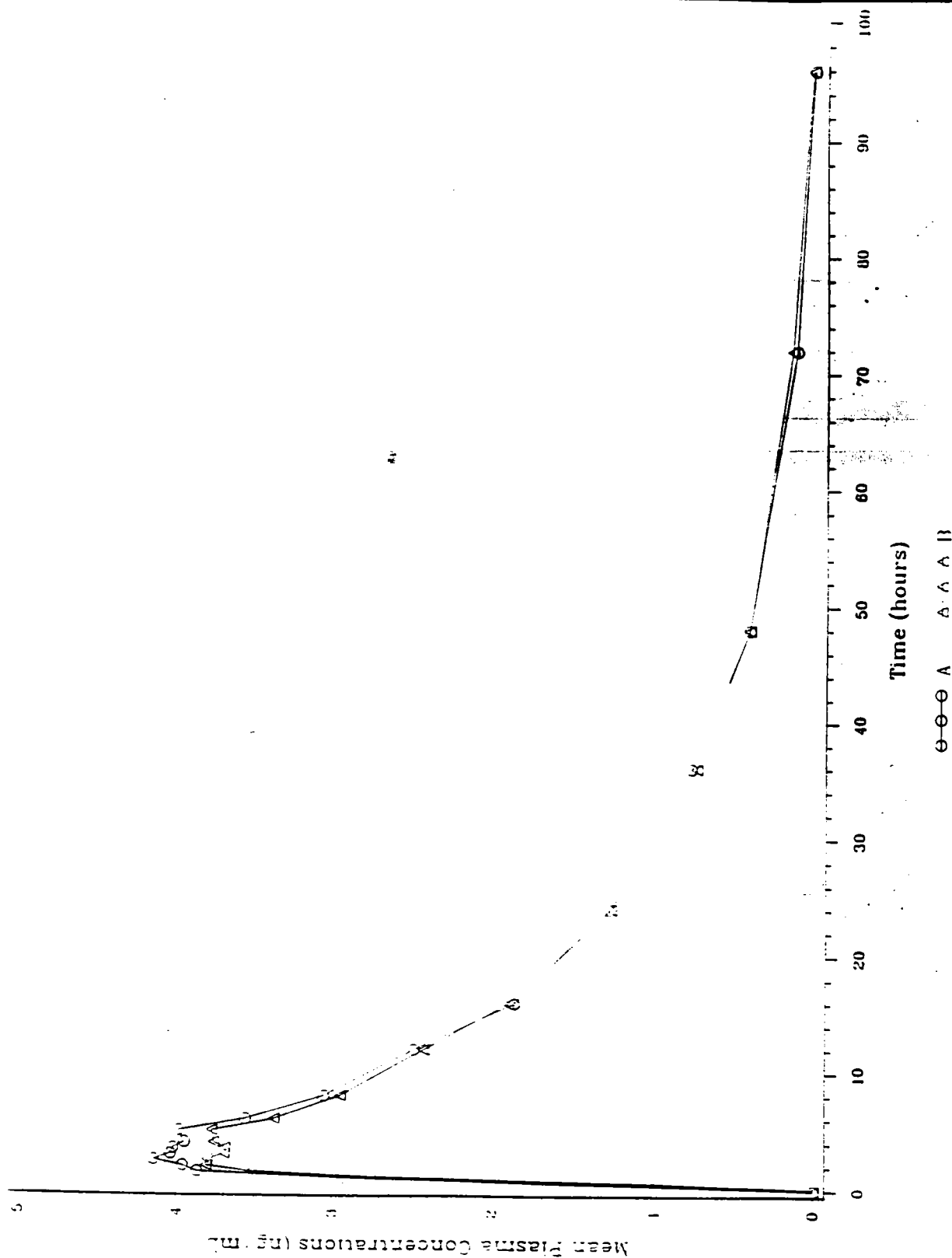


Fig. 3

GUANFACINE HCl (GUAN-9510) Mean Guanfacine Plasma Concentrations

